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## (54) Stable erythromycin solution and process therefor.

(57) A pharmaceutical formulation comprising per ml. from 1 to 100 mg. of the active ingredient erthromycin and the excipients ethanol, sufficient non-toxic acid to give a pH in the range of 8-10 after dilution with water, and propylene glycol not exceeding 0.3 ml but sufficient to bring the volume to 1 ml. The process for its preparation is described. The formulation is effective in the treatment of acne and is stable.

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# STABLE ERYTHROMYCIN SOLUTION AND PROCESS THEREFOR

Erythromycin has a limited stability in aqueous solution according to Chemical Abstracts, 60, 14337 (1964). U.S. Patent 4,000,263 discloses a stable erythromycin solution containing propylene glycol, ethyl alcohol and an ethoxylated ether of lauryl alcohol (Brij-30). The amount of propylene glycol varies from 35 to 45 percent. According to U.S. Patent 4,000,263 the erythromycin solutions disclosed therein lose about 5% of their stability in 10 weeks at 45°C. or in 18 weeks at 37°C.

Mills, writing in Cutis, 15, 93 (1975), described the use of a 2 percent solution of erythromycin in a 1:1 ethanol-water solvent for treatment of acne. J.E. Fulton Jr., Dermat, 110, 83 (1974), used a 1 percent solution of erythromycin in a solvent containing two parts of ethanol, 2 parts ethylene glycol monomethyl ether and 1 part of propylene glycol. The author reported this preparation is quite effective for the treatment of acne.

Antibiotics, including members of the lincomycin family, tetracycline and epi-tetracycline, have been used to treat acne; see U.S. Patent Nos. 3,969,516 and 3,952,099. The latter patent is more concerned with increased penetration of the antibiotic through the skin by the addition of decylmethylsulfoxide to an alcoholic solution of the antibiotic.

The invention provides a pharmaceutical formulation comprising per ml. from 1 to 100 mg. of the active ingredient erythromycin and the excipients ethanol, sufficient non-toxic acid to give a pH in the range of 8-10 after dilution with water, and propylene glycol not exceeding 0.3 ml. but sufficient to bring the volume to 1 ml.

The invention also provides a process for the preparation of a pharmaceutical formulation having as active ingredient erythromycin comprising dissolving 1 to 100 mg. per ml. final volume erythromycin in ethanol, adding sufficient non-toxic acid to give a pH in the range of 8-10 after dilution with water and adding propylene glycol in an amount of up to 30% of the final volume of the preparation. It is preferred for the ethanol to be present in an amount corresponding to 70% of the final volume of the preparation.

The preferred concentration of erythromycin in the solution is 20 mg. per ml. In the preparation of the solution sufficient acid is added to give a final pH in the range 8-10 upon dissolving the preparation in sufficient water to enable a pH reading to be taken. The pH is suitably determined on a pH meter with a glass electrode. Any pharmaceutically-acceptable non-toxic acid may be used but the preferred acid is citric acid, and it has been found that a final concentration of 0.04% of citric acid (0.4 mg/ml) gives a solution which upon dilution in water yields of pH of about 9 with a glass electrode.

A double-blind study was carried out in humans suffering from acne in which the vehicle itself lacking the erythromycin was used as a control. Those patients receiving a formulation made in accordance with this invention showed a 56% decrease in the number of papules over the test period whereas in the control group which received the formulation vehicle alone there was only a 31% decrease in papules. The number of patients used were sufficient to render this difference statistically significant.

The solutions of this invention are quite stable. For example, a solution containing 22 mg of erythromycin (10% excess), 0.7 ml of ethanol USP, sufficient citric acid to give a final concentration of 0.04% and propylene glycol q.s to 1 ml. was shown to assay 83.2% of initial (92.9% of label claim) antibiotic present at 25°C. after thirty months storage. Other solutions confirm this trend in stability.

In preparing the erythromycin solution of this invention, it is customary to dissolve the erythromycin base and acid, e.g. organic acid, preferably citric acid, in ethanol and then add sufficient propylene glycol to make up the final solution to 1 ml. or a multiple thereof. The ingredients are then thoroughly mixed.

Whilst the propylene glycol can be present in an amount of up to 30% of the total volume of formulation (0.3 ml per ml), it is preferably present in an amount which itself is at least sufficient to dissolve the erythromycin contained in the formulation so that the erythromycin is kept in solution and available for absorption into the skin upon any evaporation of the ethanol. Amounts of above 30% propylene glycol tend to cause skin irritation. The ethanol is likewise preferably present in an amount at least sufficient to dissolve the erythromycin contained in the formulation.

## CLAIMS

1. A pharmaceutical formulation comprising per ml. from 1 to 100 mg. of the active ingredient erythromycin and the excipients, ethanol, sufficient non-toxic acid to give a pH in the range of 8-10 after dilution with water, and propylene glycol not exceeding 0.3 ml but sufficient to bring the volume to 1 ml.

2. A pharmaceutical formulation according to Claim 1 wherein the non-toxic acid is citric acid.

3. A pharmaceutical formulation according to Claim 1 wherein the non-toxic acid is citric acid and the amount of citric acid present is about 0.4 mg. per ml.

4. A pharmaceutical formulation according to any preceding claim wherein 20 mg. per ml. erythromycin is present.

5. A pharmaceutical formulation according to any preceding claim wherein 0.7 ml per ml. ethanol is present.

6. A process for the preparation of a pharmaceutical formulation having as active ingredient erythromycin comprising dissolving 1 to 100 mg. per ml final volume erythromycin in ethanol, adding sufficient non-toxic acid to give a pH in the range of 8-10 after dilution with water and adding propylene glycol in an amount of up to 30% of the final volume of the formulation.

7. A process according to claim 6, wherein the ethanol is employed in an amount corresponding to 70% of the final volume of the formulation.

8. A process according to Claim 6 or 7 wherein the non-toxic acid is citric acid.

9. A process according to Claim 6,7 or 8 wherein 20 mg. per. ml. final volume erythromycin is dissolved.

10. A liquid pharmaceutical formulation comprising:

A) erythromycin in an amount of from 1 to 100 mg. per ml of formulation,

B) ethanol in an amount at least sufficient in itself to dissolve the amount of erythromycin contained in the formulation,

C) propylene glycol again in an amount at least sufficient in itself to dissolve the amount of erythromycin contained in the formulation, subject to the proviso that the propylene glycol is present in an amount not exceeding 30% by volume of the formulation and

D) a non-toxic acid in an amount sufficient to give a pH in the range of 8-10 after dilution of the formulation in sufficient water to enable a pH reading to be obtained